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Psoriasis treat to target: defining outcomes in psoriasis using data from a real world, population-based cohort study (the British Association of Dermatologists Biologics and Immunomodulators Register, BADBIR)

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Abstract

Background: The 'treat to target' paradigm improves outcomes and reduces costs in chronic disease management but is not yet established in psoriasis.

Objective: To identify treatment targets in psoriasis using the common measures of disease activity: Psoriasis Area and Severity Index (PASI) and Physician Global Assessment (PGA).

Methods: Data from a multicentre longitudinal UK cohort of psoriasis patients receiving systemic/biologic therapies (British Association of Dermatologists Biologics and Immunomodulators Register) were used to identify absolute PASI thresholds for 90% (PASI 90) and 75% (PASI 75) improvements in baseline disease activity, using receiver operating characteristic curves. The relationship between PGA (clear/almost clear/mild/moderate/moderate-severe/severe) and PASI (range 0-72) was described, and the concordance between absolute and relative definitions of response was determined. The same approach was used to establish treatment response and eligibility definitions based on PGA.

Results: Data from 13,422 patients were available (58% male, 91% white ethnicity, mean age 44.9 years), including over 23,000 longitudinal PASI and PGA scores. An absolute PASI < 2 was concordant with PASI 90 and an absolute PASI < 4 was concordant with PASI 75 in 90% and 88% of cases, respectively. These findings were robust to subgroups of timing of assessment, baseline disease severity and treatment modality. PASI and PGA were strongly correlated (Spearman's rank correlation coefficient 0.92). The median PASI increased from 0 (IQR 0-0, range 0-23) to 19 (IQR 15-25, range 0-64) for PGA clear to severe, respectively. PGA clear/almost clear was concordant with PASI < 2 in 90% of cases, and PGA moderate-severe/severe was concordant with NICE PASI eligibility criteria for biologics in 81% of cases.

Conclusions: An absolute PASI < 2 and PGA clear/almost clear represent relevant disease endpoints to inform treat to target management strategies in psoriasis.

Introduction

Psoriasis is a chronic, inflammatory skin disease that is recognised as a major global health problem by the World Health Organization and affects 2-4% of the population (1). It is associated with reduced quality of life and multiple morbidities including psoriatic arthritis, cardiovascular disease, obesity and depression (2). Recent insights into the molecular pathogenesis of psoriasis have led to the development of increasingly effective targeted therapies, which have transformed patient and clinician expectations of treatment (3), and improved co-morbidity outcomes (4). In this context, a robust target disease activity endpoint is needed to drive the introduction and modification of treatments in a timely, effective and cost-efficient manner. This 'treat to target' paradigm is well

established in cardiology (hypertension, hyperlipidaemia), endocrinology (diabetes mellitus) and rheumatology (rheumatoid arthritis), and can improve patient outcomes and reduce costs (5,6).

In psoriasis, the disease activity endpoint is currently defined by a relative change from baseline rather than an absolute measure, using the psoriasis area severity index (PASI; range 0-72) (6–8). PASI 75 (a 75% improvement in PASI from baseline) and increasingly, PASI 90, are common primary endpoints in interventional clinical trials (7) and parallel clinically relevant improvements in patient-reported outcomes (dermatology life quality index [DLQI] 0 or 1) (8). These endpoints have driven treatment guideline recommendations on eligibility and response to psoriasis interventions (9,10). In clinical practice however, the accuracy and relevance of relative (in contrast to absolute) PASI measures is limited by a dependence on the baseline PASI. This may have been established historically or be uncertain due to the chronic nature of the disease and variability in washout of prior systemic therapies. There is also potential for inter-assessor variability of current versus baseline PASI measurements.

Aside from difficulties related to use of a baseline assessment to inform a treatment target, there are also limitations with the measure itself. Separate calculations of extent and intensity of plaques of psoriasis at four anatomical regions (head, trunk, upper and lower extremities) may be challenging in time-pressed routine practice (11) and introduce potential for inter-assessor variation and calculation errors. There is limited sensitivity for evaluating patients with low levels of disease, redundancy at the upper half of the range for PASI and a paucity of data on the utility of PASI in real-world as opposed to trial settings (12). The physician global assessment (PGA) may be a useful alternative measure for daily practice, since it is a simple, average assessment of all psoriasis lesions according to a Likert scale (6 point score in European Medicines Agency [EMA] guidelines; clear/almost clear/mild/moderate/moderate-severe/severe) (13). However, there has been no formal assessment of its utility with respect to PASI in routine practice.

In this study, we use a large-scale real-world multicentre longitudinal cohort of patients receiving systemic therapies (the British Association of Dermatologists Biologics and Immunomodulators Register; BADBIR) (14) to establish an absolute definition of disease control based on the most widely used relative measure PASI 90. The clinical utility of PGA is investigated by determining the relationship between PASI and PGA, and exploring how this relates to current PASI-based definitions of treatment eligibility and response using the UK exemplar NICE criteria (9).

Methods

Study design and setting

This study uses data from BADBIR, which is a UK and Republic of Ireland multi-centre pharmacovigilance registry (REC ref: 07/MRE08/9). BADBIR was established in 2007 for individuals with psoriasis starting on systemic therapies, aged 16 years or older, and is described in detail elsewhere (14–16). It includes detailed demographic and longitudinal clinical data on all participants including regular multimodal disease severity and treatment outcome measurements such as PASI and PGA. Baseline assessments are completed within the first 6 months of treatment (-183 to 0

days) and follow up visits are at 6 monthly intervals for the first 3 years and then annually to 10 years. The data cut for this analysis is 1st April 2018.

Individuals with a diagnosis of psoriasis under the care of a dermatologist, started on or switched to a biologic (for the 'biologic cohort') or non-biologic systemic therapy (for the 'non-biologic systemic cohort') within the previous 6 months and able to give informed consent are eligible for inclusion. Individuals in the 'non-biologic systemic cohort' have a PASI ≥ 10 and DLQI >10 (unless switching between non-biologic systemic agents) and have no prior exposure to a biologic agent (14). There is no minimum PASI or DLQI inclusion criteria for participants in the 'biologic cohort' as biologic therapy eligibility according to NICE criteria (PASI > 10 and DLQI > 10) is assumed (9).

Outcome measures

PASI scores are measured consecutively over time for each participant and the primary outcome measure of treatment response is defined as PASI 90 (a 90% improvement in PASI from baseline), which is the most widely used standard primary outcome in psoriasis. PASI 75 response is analysed as a secondary outcome.

Statistical methods

Identifying an absolute PASI threshold which corresponds to PASI 90 and PASI 75

Receiver operating characteristic (ROC) curves are used on the longitudinal PASI data in BADBIR to establish absolute PASI thresholds corresponding to PASI 90 and PASI 75 responses. Individuals with a missing baseline PASI are not included. Since PASI 90 and PASI 75 are calculated with respect to baseline PASI, mathematical coupling (17) between the relative and absolute PASI would inflate the statistical measures derived from the ROC curve. Therefore, ROC curves are used to inform cutpoint locations based on maximising the sum of sensitivity and specificity with bootstrap estimation (100 bootstrap replications). Contingency tables then identify clinically relevant cutpoints within the identified locations. Cohen's kappa is used to quantify agreement with PASI based definitions. This statistic is inflated due to the definitions of response being based on the same PASI value, so should be treated with caution. Cohen's kappa 0.41-0.6, 0.61-0.80 and >0.8 indicate moderate, substantial and almost-perfect agreements, respectively.

Sensitivity analyses investigate the impact of treatment (biologic versus non-biologic systemic agents), timing of assessment (6 months versus 12 months following start of treatment; 2013-2015 versus 2016-2018; baseline PASI assessment on treatment start date versus prior to treatment start date) and baseline disease severity (PASI <10, 10-20, >20). The time periods 2013-2015 and 2016-2018 are selected to assess for any effect of the recent introduction of more efficacious biologic agents.

Exploring the relationship between PASI and PGA, and establishing PGA response and eligibility definitions

The relationship between PASI and PGA is assessed graphically using box and whisker plots and quantified using Spearman's rank correlation coefficient. The approach described above is used to evaluate the potential impact of changing from PASI to PGA in clinical practice. We thus use the absolute PASI threshold corresponding to the most commonly used relative PASI definition of treatment response (PASI 90 (13)) and PASI-based NICE criteria for biologics eligibility (PASI > 10 (9)) to derive PGA-based definitions for response and biologic eligibility. Cohen's kappa is used to quantify agreement between PASI- and PGA-based definitions. All patients included in the analysis have both a PGA and PASI recorded on the same day post-baseline. All analyses are on a complete case basis and conducted in Stata 15 (18).

Results

Cohort characteristics

Data from 13,422 patients with psoriasis enrolled in BADBIR are included. Of these, 9,201 patients received a biologic agent ('biologic cohort') and 4,221 patients received a non-biologic systemic treatment ('non-biologic systemic cohort') (Table 1, Supplementary Table 1). 1,371 patients switched from the non-biologic systemic cohort to the biologic cohort and are therefore included in the analysis twice. Hence, data from 12,051 patients are unique. Patients had consecutive outcome assessments performed over a median of 338 days (inter-quartile range [IQR] 252-386, range 0-7530).

The baseline characteristics of the participants are listed in Table 1 and are in line with those from previous reports (15,19). The average baseline PASI is 15.4 (standard deviation [sd] 8.1) and 58.3% are male. The average age and body mass index of participants are 44.9 years (sd 13.5 years) and 30.8 kg/m^2 (sd 7.2 kg/m^2), respectively. Almost all participants have chronic plaque psoriasis (98.8%) and 18.9% have concurrent psoriatic arthritis.

PASI ≤ 2 is consistent with PASI 90 response

Response status (i.e. responder/non-responder) is assigned according to PASI 90 status. The relative PASI response is derived from 23,501 longitudinal PASI measurements in 10,894 patients, in which each patient has a baseline PASI and at least one follow-up PASI recorded. When balancing sensitivity and specificity, the ROC curve analysis indicates that an absolute PASI threshold around 1.6 (95% confidence interval (CI) 1.5, 1.7) is consistent with PASI 90 responses. To optimise potential practical utility, we explored absolute PASI thresholds of 2 and 1.5 (Table 2a).

PASI ≤ 2 assigns the same response status as PASI 90 in 90% of cases with a Cohen's kappa of 0.78 (95% CI 0.77, 0.79), indicating substantial agreement (Table 2a, Figure 1a). PASI < 1.5 assigns the same response status as PASI 90 in 93% of cases (Cohen's kappa 0.85 (95% CI 0.84, 0.86)), however 3% of cases are classified as non-responders using PASI < 1.5 but are responders according to PASI

90 status. This reduces to 1% using PASI < 2, indicating a more frequent correct assignment of PASI 90 response status (i.e. fewer false negative classifications) with this higher absolute threshold. These PASI 90 responders who are classified as non-responders according to an absolute PASI threshold of 2 necessarily have more severe disease (mean baseline PASI 34.2 (sd 8.3) versus mean baseline PASI 15.7 (sd 8.1) for the whole cohort).

4% of cases are classified as responders using PASI ≤ 1.5 but are non-responders according to PASI 90. This increases to 9% for PASI ≤ 2 since this higher threshold is more liberal for assigning responder status. Cases classified in this way using PASI < 2 necessarily have milder disease pre-treatment (mean baseline PASI 10.1 (sd 4.2) versus mean baseline PASI 15.7 (sd 8.1) for the whole cohort). This highlights the inherent mathematical constraints of achieving a relative PASI 90 response with a low baseline PASI.

PASI < 4 is consistent with PASI 75 response

The ROC curve analysis indicates that an absolute PASI threshold around 3.3 (95% CI 3.0, 3.5) is concordant with PASI 75 responses. We therefore explored more practical absolute definitions of PASI ≤ 3, PASI ≤ 3.5 and PASI ≤ 4 (Table 2b, Figure 1b). By applying the same logic as described above for PASI 90, an absolute PASI ≤ 4 is identified as concordant with PASI 75. The agreement between PASI 75 and PASI ≤ 4 is 88% with a Cohen's kappa 0.76 (0.75, 0.77).

PASI correlates with PGA

PASI and PGA are both recorded on the same day on 23,475 occasions in 11,501 patients. There is a strong positive Spearman's Rank correlation coefficient of 0.92 between PASI and PGA (Figure 2), as the median PASI decreases progressively from 19.2 (interquartile range (IQR) 14.6, 25) for PGA severe, to 0 (IQR 0, 0) for PGA clear (Supplementary Table 2). There is, however, large variability in the PASI score within each PGA category since the range of PASI values overlaps across PGA categories (Figure 2).

PGA clear or almost clear can be used interchangeably with PASI ≤ 2

PASI ≤ 2 is consistent with PGA clear or almost clear in 90% of cases, with a Cohen's kappa of 0.79 (95% CI 0.78, 0.80), indicating substantial agreement (Table 3a, Figure 3a). PASI ≤ 4 is concordant with PGA mild or better (i.e. PGA mild, almost clear or clear) in 90%, with a Cohen's kappa of 0.77 (95% CI 0.77, 0.78), indicating substantial agreement (Table 3b).

PGA moderate-severe or severe is equivalent to NICE biologics eligibility criteria of PASI ≥ 10

PASI and PGA are both recorded at baseline in 10,154 patients. In 81% of cases PGA moderate-severe or severe is consistent with PASI-based NICE eligibility criteria for biologic therapy (PASI ≥ 10) (Table 4, Figure 3b). The Cohen's kappa of 0.46 (95% CI 0.44, 0.48) indicates moderate agreement. In 3%, eligibility would be gained under this PGA-based definition, despite not satisfying current PASI-based criteria. Conversely, 15% with PASI ≥ 10 would become ineligible for biologics according to this PGA definition.

Sensitivity analyses show that all results are robust to type of treatment, timing of assessments, and baseline PASI (Supplementary Table 3).

Discussion

Key findings

This study is the first real-world systematic evaluation of absolute measures of disease control in psoriasis to date and is thus relevant for routine clinical practice, trials investigators and regulatory agencies. Using a multi-centre cohort of more than 13,000 patients, we demonstrate that an absolute PASI < 2 corresponds with PASI 90 responses and is a relevant disease endpoint for treat to target approaches in psoriasis, obviating the need for baseline disease severity measurements. We also show that PASI and PGA are strongly correlated, and propose PGA moderate-severe/severe as an alternative eligibility criterion to PASI-based definitions for biologics, and PGA clear/almost clear as an appropriate treatment endpoint.

Comparisons with the current literature

Our study serves as the first validation of growing expert opinion supporting the use of absolute rather than relative measures of disease severity as treatment endpoints in psoriasis (10,20). A recent consensus opinion paper based on the Delphi methodology proposed that absolute PASI < 2 should be the pursued PASI goal, since it was felt to correlate better than relative PASI with the health related quality of life measure DLQI (21). Our data support current trends in trial practices, whereby the proportion of patients achieving absolute PASI values is increasingly reported as secondary endpoints due to the recognition that these values may be more clinically meaningful than relative PASI measures (22,23).

In daily practice, where baseline PASI is often lower than in clinical trials due to switching between systemic agents, achieving a PASI 90 response has been shown to represent an unrealistic treatment goal. A recent multi-centre prospective study using the BioCAPTURE Dutch cohort showed that an absolute PASI ≤ 2 was more often achieved than PASI 90 at week 24 of biologic therapy (24.2% versus 14.8%, respectively) (24). This real-world relative PASI response rate is substantially lower than those reported in randomised controlled trials of the same biologics (adalimumab, etanercept, infliximab, ustekinumab), in which PASI 90 was achieved in 20–58% of patients at weeks 16–28 (25–

28). This underscores the relevance of absolute disease scores for defining clinically viable treat to target strategies (as derived in our study), and holds great promise for improving real-world patient outcomes.

Since the limitations of the PASI are well recognised (29,30), the EMA and Food and Drug Administration recommend that it is used in conjunction with PGA for assessing efficacy and informing licensing of new treatments (13,31). Clinicians are facing increasing time and resource pressures, in the context of a rising global prevalence of psoriasis (1,32), so PGA is often used in preference to PASI measurements in real-world settings. We validate this approach by demonstrating a close correlation between PGA and PASI, irrespective of treatment modality. This substantiates findings from a meta-analysis of 30 randomised controlled trials of biologic agents in moderate-severe psoriasis (using varying PGA Likert scales), which demonstrated a correlation coefficient of 0.916 ($p<0.01$) between PASI 75 responses and PGA clear or almost clear for study weeks 8-16 (30). Assessment of PASI 90 responses was not within the scope of the meta-analysis, however PASI 90 has been subsequently shown to significantly correlate with an investigator global assessment (6 point Likert scale) of clear or almost clear in a phase 2b trial of secukinumab 150mg monthly dosing (48.1% clear/almost clear and 51.9% PASI 90 at week 12) (33). Given that PGA clear or almost clear correctly classifies nearly all PASI 90 responses in our real-world dataset, the use of PGA clear/nearly clear may be a justified descriptor of PASI 90 in routine practice.

Our proposed eligibility criterion for biologic therapy of PGA moderate-severe/severe is in keeping with US guidelines (12) and could be rapidly adopted into daily clinical practice due to the ease of measurement of categorical as opposed to quantitative variables. We have used the UK healthcare model to explore the potential impact of switching to the PGA. Despite not accounting for the extent of body surface involvement, our PGA-based eligibility criterion would not result in a substantial increase in the number of eligible patients compared with the PASI-based criterion used in current UK guidelines (9), and therefore would not be expected to have a major impact on current cost effectiveness modelling for biologic therapies. However, since 15% of eligible cases become ineligible for a biologic using this PGA criterion, we propose that either PGA moderate-severe/severe or PASI > 10 are considered eligibility criteria in routine practice. Importantly, according to our proposed PGA criterion, individuals may be considered for biologic therapy if they have a lower PASI but severe, localised disease on sites that are associated with high functional impairment or distress (e.g. face, genitals) (34).

Strengths and limitations

The major strengths of the study are the large sample size, high external validity conferred by the participation of multiple centres across the UK and Republic of Ireland (14) and fully independent data analysis. Detailed data capture occurred at any point in the treatment cycle, spanned a wide time frame (2005-2018) and allowed for analysis of both non-biologic systemic and biologic therapies, which maximises the generalisability of our findings.

The limitations of the study include the predominant inclusion of patients with moderate to severe disease since the dataset relates to individuals qualifying for or already receiving a systemic agent. Correlation with patient-reported measures such as DLQI was out of the scope of this study. Data were collected for other purposes, such as to justify commencing a biologic agent, which may introduce potential distortions in the dataset e.g. inflated baseline severity score. Generalisability of our PGA data is limited by a lack of a universal adoption of a single PGA score in routine practice, clinical trials or by regulatory agencies (35). However, most do employ the 6 point score to rate disease severity from 'clear' to 'severe' that was used for our study (13,31).

Since it is likely that the PGA and PASI are simultaneously measured by the same assessor, the concordance between these scores may be inflated, as the first measurement may bias the second. The order in which the PASI and PGA are measured may also therefore be relevant. The potential influence of these factors on our results is, however, limited by the consecutive measurement of scores throughout the treatment cycle for each individual.

Finally, our dataset is based on the currently available systemic and biologic therapies for psoriasis, however the therapeutic armamentarium for psoriasis is undergoing a rapid expansion, with several agents recently approved for use or awaiting imminent approval (3). Since these newer agents offer comparable or better efficacy rates compared with the analysed treatments, our proposed stringent endpoints are likely to remain relevant. We also demonstrated the robustness of our findings in different time windows, thereby indicating negligible influence of drug class.

Summary and clinical implications

Since skin clearance or near clearance is now a realistic outcome of treatment, irrespective of baseline disease severity, this study proposes up to date treatment goals based on real-world data. We demonstrate that an absolute PASI < 2 is a relevant and practical disease endpoint in psoriasis, which could be used to define treat to target approaches in routine clinical settings. If adopted, this paradigm shift in psoriasis care would align clinical practice with that of other chronic diseases such as diabetes and hypertension, wherein patients are treated to the goal of 'normalisation' in order to prevent end organ damage (e.g. cardiac events (36)). Our data also highlight PGA severity scores as alternatives to PASI for treatment eligibility criteria and measures of response, which is likely to be highly clinically viable. Future analysis of patient and clinician acceptability of our proposed criteria will yield additional important data on clinical utility.

What's already known about this topic?

- The most commonly used relative disease activity measure in psoriasis is PASI 90, however it has several limitations including dependency on a baseline severity assessment.

- Defining an absolute target disease activity endpoint in psoriasis has the potential to improve patient outcomes and reduce costs, as demonstrated by treat to target approaches in other chronic diseases such as hypertension and diabetes.
- The PGA is a popular alternative measure of psoriasis severity in daily practice however its utility has not been formally assessed with respect to PASI.

What does this study add?

- An absolute PASI < 2 corresponds with PASI 90 responses and is a relevant disease endpoint for treat to target approaches in psoriasis.
- There is a strong correlation between PASI and PGA.
- PGA moderate-severe/severe may serve as an alternative eligibility criterion for biologics to PASI-based definitions, and PGA clear/almost clear is an appropriate alternative absolute treatment endpoint.

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Table 1: Baseline characteristics of the BADBIR cohort.

	Biologic cohort (n=9201)	Non-biologic systemic cohort (n=4221)	Overall (n=13422*)
Disease duration (years), mean (SD)	21.7 (12.6) (n=9134)	18.7 (13.3) (n=4202)	20.7 (12.9) (n=13336)
Age of onset (years), mean (SD)	23.3 (13.5) (n=9185)	25.5 (15.3) (n=4216)	24.0 (14.1) (n=13401)
Baseline PASI score, mean (SD)	15.7 (8.1) (n=7948)	14.8 (8.0) (n=3957)	15.4 (8.1) (n=11905)
Baseline DLQI score, mean (SD)	17.4 (7.7) (n=4683)	15.6 (7.1) (n=3054)	16.7 (7.5) (n=7737)
Baseline PGA score			
Severe	2111 (32.1%)	870 (24.2%)	2981 (29.3%)
Moderate-Severe	2869 (43.6%)	1510 (42.0%)	4379 (43.0%)
Moderate	1312 (19.9%)	924 (25.7%)	2236 (22.0%)
Mild	180 (2.7%)	198 (5.5%)	378 (3.7%)
Almost Clear	81 (1.2%)	71 (2.0%)	152 (1.5%)
Clear	31 (0.5%)	20 (0.6%)	51 (0.5%)
	(n=6584)	(n=3593)	(n=10177)
Sex male	5455 (59.3%) (n=9201)	2366 (56.1%) (n=4221)	7821 (58.3%) (n=13422)
White ethnicity	8391 (91.4%) (n=9179)	3800 (90.4%) (n=3800)	12191 (91.1%) (n=13381)
Age (years), mean (SD)	45.1 (13.1) (n=9201)	44.3 (14.4) (n=4221)	44.9 (13.5) (n=13422)
BMI (kg/m2), mean (SD)	31.1 (7.2) (n=8585)	30.2 (7.1) (n=3912)	30.8 (7.2) (n=12497)
BMI categories (kg/m2)			
Underweight (BMI<18.5)	71 (0.8%)	56 (1.4%)	127 (1.0%)
Normal weight (18.5-24.9)	1530 (17.8%)	864 (22.1%)	2394 (19.2%)
Overweight (25.0-29.9)	2718 (31.7%)	1296 (33.1%)	4014 (32.1%)
Obese class I (30.0-34.9)	2154 (25.1%)	900 (23.0%)	3054 (24.4%)
Obese class II (35.0-39.9)	1199 (14.0%)	423 (10.8%)	1622 (13.0%)
Obese class III (40.0-more)	913 (10.6%)	373 (9.5%)	1286 (10.3%)
	(n=8585)	(n=3912)	(n=12497)
Smoking status			
Never smoked	2724 (34.0%)	1124 (30.3%)	3848 (32.8%)
Previous smoker	2902 (36.2%)	1328 (35.8%)	4230 (36.1%)
Current smoker	2393 (29.8%)	1259 (33.9%)	3652 (31.1%)
	(n=8019)	(n=3711)	(n=11730)
Chronic plaque psoriasis	9098 (98.9%) (n=9201)	4169 (98.8%) (n=4221)	13267 (98.8%) (n=13422)
PsA at baseline	2096 (22.8%) (n=9201)	441 (10.4%) (n=4221)	2537 (18.9%) (n=13422)
Other type(s) of psoriasis (erythrodermic, guttate, generalised pustular, localised pustular or unstable)	2210 (24.1%) (n=9169)	1105 (26.2%) (n=4214)	3315 (24.8%) (n=13383)

* 1,371 patients switched from a non-biologic systemic to a biologic agent so are included in these summaries twice. There are therefore 12,051 unique patients overall.

Table 2: Comparison of absolute PASI definitions of response with (a) PASI 90 and (b) PASI 75.
These data are derived from 23,501 PASI measurements in 10,894 patients.

(a)

		PASI 90	
		No	**Yes**
PASI ≤ 1.5	**No**	14,817 (63%)	606 (3%)
	Yes	979 (4%)	7,099 (30%)
PASI ≤ 1.6	**No**	14,622 (62%)	506 (2%)
	Yes	1,174 (5%)	7,199 (31%)
PASI ≤ 2	**No**	13,619 (58%)	236 (1%)
	Yes	2,177 (9%)	7,469 (32%)

For PASI 90 and PASI ≤ 2: Agreement 90%, Cohen's kappa 0.78 (0.77, 0.79).

(b)

		PASI 75	
		No	**Yes**
PASI ≤ 3	**No**	9,814 (42%)	1,386 (6%)
	Yes	1,105 (5%)	11,196 (48%)
PASI ≤ 3.3	**No**	9,532 (41%)	1,092 (5%)
	Yes	1,387 (6%)	11,490 (49%)
PASI ≤ 3.5	**No**	9,359 (40%)	951 (4%)
	Yes	1,560 (7%)	11,631 (49%)
PASI ≤ 4	**No**	8,737 (37%)	582 (2%)
	Yes	2,182 (9%)	12,000 (51%)

For PASI 75 and PASI ≤ 4: Agreement 88%, Cohen's kappa 0.76 (0.75, 0.77).

Table 3: Comparison of PGA definitions of response with proposed absolute PASI definitions of response. These data are derived from 23,475 occasions in which PASI and PGA are both recorded on the same day in 11,501 patients.

(a)

		PASI ≤ 2	
		No	**Yes**
PGA Clear or Almost Clear	**No**	12,084 (51%)	824 (4%)
	Yes	1,572 (7%)	8,995 (38%)

Agreement 90%, Cohen's kappa 0.79 (0.78, 0.80).

(b)

		PASI ≤ 4	
		No	**Yes**
PGA Clear, Almost Clear or Mild	**No**	7,175 (31%)	407 (2%)
	Yes	2055 (9%)	13838 (59%)

Agreement 90%, Cohen's kappa 0.77 (0.77, 0.78).

Table 4: Comparison of PASI-based NICE biologics eligibility criterion (PASI ≥ 10) with PGA-based eligibility criterion. These data are derived from 10,154 patients, in which PASI and PGA are both recorded at baseline.

		PASI ≥ 10	
		No	**Yes**
PGA Moderate-Severe or Severe	**No**	1,255 (12%)	1,557 (15%)
	Yes	338 (3%)	7,004 (69%)

Agreement 81%, Cohen's kappa 0.46 (0.44, 0.48).

Figure 1: Agreement between (a) PASI 90 and PASI ≤ 2, (b) PASI 75 and PASI ≤ 4. The blue segment represents the agreement between the two definitions and the grey segment represents the disagreement. These data are derived from 23,501 longitudinal PASI measurements in 10,894 patients.

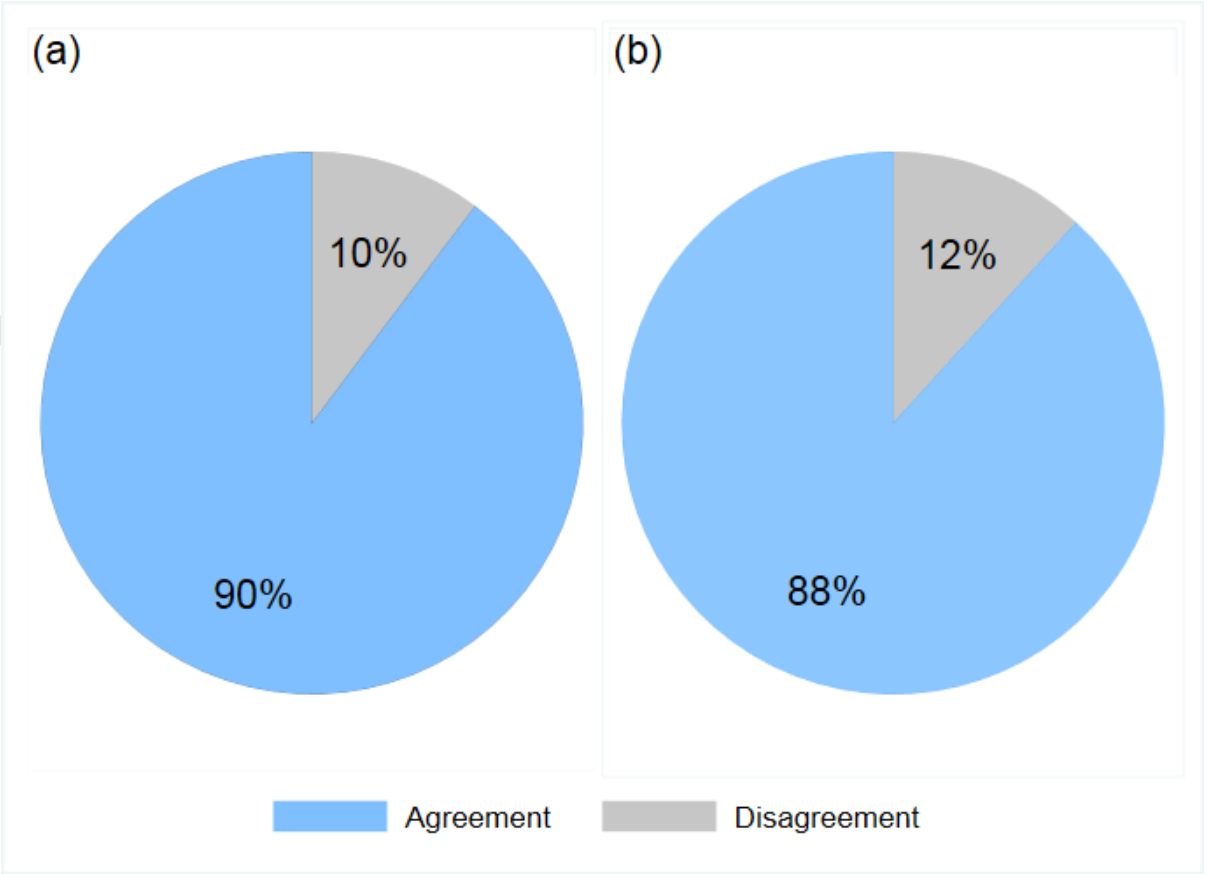

Figure 2: Correlation between PGA and PASI. These data are derived from 23,475 occasions in 11,501 patients in which PASI and PGA are both recorded on the same day.

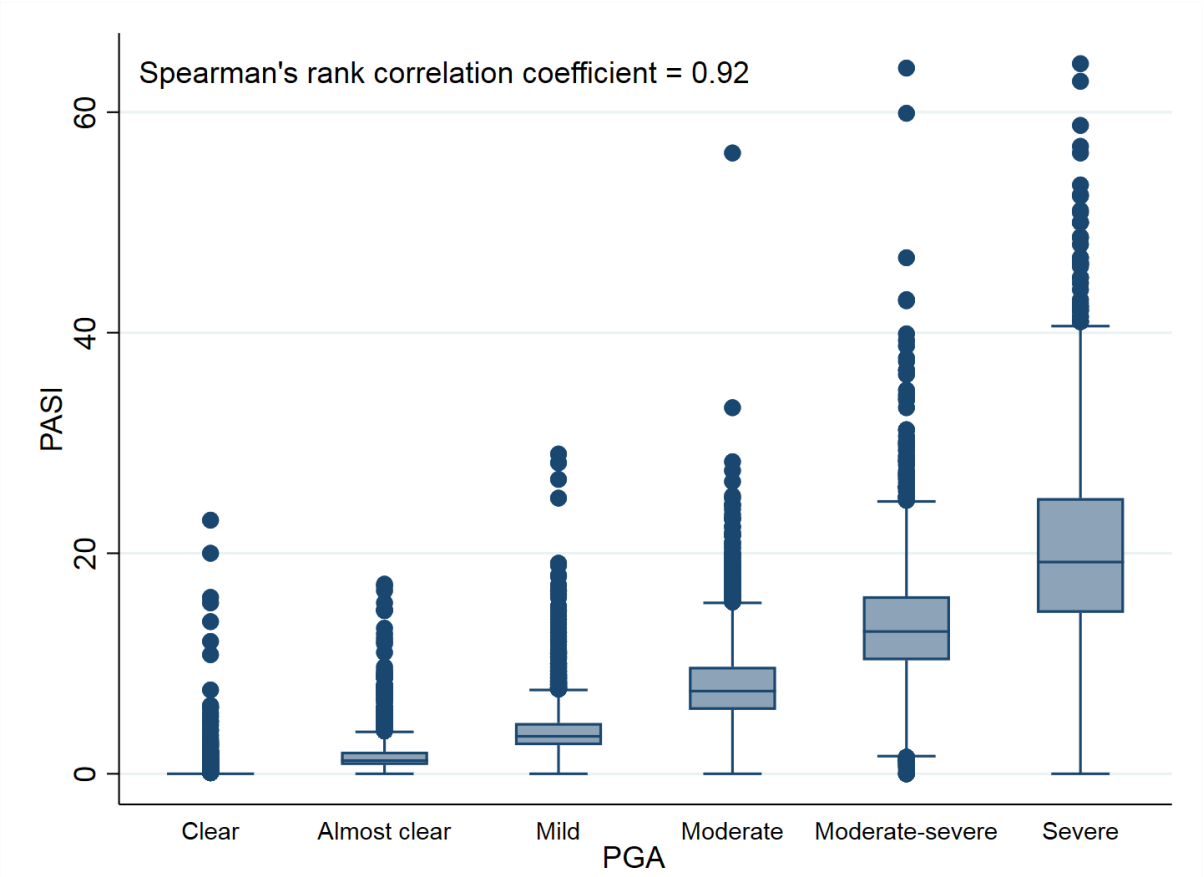

Figure 3: Agreement between (a) PGA Clear/Almost Clear and PASI ≤ 2 and (b) PGA Moderate-Severe/Severe and PASI ≥ 10. The blue segment represents the agreement between the two definitions and the grey segment represents the disagreement. Data in (a) are derived from 23,475 occasions in 11,501 patients in which PASI and PGA are both recorded on the same day. Data in (b) are derived from 10,154 patients in which PASI and PGA are both recorded at baseline.